REMARKS

I. Rejection of Claims 1, 2, 13, and 14 Under 35 U.S.C. § 101

SUMMARY OF THE INVENTION

Applicants' invention is directed, *inter alia*, to an isolated polypeptide ("HSEBP") having strong homology to human fetal heart selenium-binding protein (G1374792; SEQ ID NO:3), mouse liver selenium-binding protein (G227630; SEQ ID NO:4), and mouse liver acetaminophen-binding protein (G298710; SEQ ID NO:5). The claimed polypeptide has a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of HSEBP, for toxicology testing, and for drug discovery. (See the Specification at, e.g., page 1, line 20 through page 3, line 24, page 24, line 34 through page 25, line 31, page 33, line 28 through page 34, line 15, and page 38, lines 9-27.) As described in the Specification (page 12, line 8 through page 13, line 6):

> The invention is based on the discovery of a novel human selenium-binding protein (HSEBP), the polynucleotides encoding HSEBP, and the use of these compositions for the diagnosis, prevention or treatment of conditions and diseases such as liver necrosis, and kidney or lung damage resulting from chemical toxicity, as well as liver, kidney, lung, mammary, epithelial, gastrointestinal, and endocrine cancer.
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> Nucleic acids encoding the HSEBP of the present invention were first identified in Incyte Clone 989953 from the colon cDNA library (COLNNOT11) through a computer-generated search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:2, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 989953 (COLNNOT11), 609011, 1226183, and 1227155 (COLNNOT01), 1334268 (COLNNOT13), 1284686 (COLNNOT16), 1391936 (THYRNOT03), (COLNNOT01), 959734 (BRSTTUT03), 892480 (STOMTUT01), and 814959 (OVARTUT01).
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> In one embodiment, the invention encompasses the novel human selenium-binding protein, a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Fig. 1A,B,C. HSEBP is 472 amino acids in length and has no predicted transmembrane domains, potential glycosylation or phosphorylation sites. HSEBP is enriched in leucine and glycine residues which together constitute more than 20% of the total amino acid content. As shown in Fig. 1A,B,C, there are no in-frame TGA termination codons in the nucleic acid sequence of SEQ ID NO:2 to direct the incorporation of selenocysteine into the protein of SEQ ID NO:1. HSEBP has

chemical and structural homology with the human fetal heart selenium-binding protein (G1374792; SEQ ID NO:3), mouse liver selenium-binding protein (G227630; SEQ ID NO:4), and mouse liver acetaminophen-binding protein (G298710; SEQ ID NO:5). In particular, HSEBP shares 96%, 86%, and 88% identity, respectively, with each of these proteins. As illustrated by Figs. 3 and 4, HSEBP and human fetal heart selenium-binding protein have rather similar hydrophobicity plots. Their isoelectric points, 5.91 and 6.13, respectively, are also similar. Northern analysis (Fig. 5) shows the expression of the HSEBP sequence in various libraries. Approximately 50% of these libraries are from cancerous tissues and 38% are from the gastrointestinal tract.

Claims 1, 2, 13, and 14 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that "the invention is not supported by either a specific asserted utility or a well established utility." (Office Action, page 2.)

The rejection of Claims 1, 2, 13, and 14 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as human selenium-binding protein, abbreviated as HSEBP, is a polypeptide encoded by a gene that is expressed in human colon tissue. The novel polypeptide is demonstrated in the specification to be a member of the class of selenium-binding proteins, whose biological functions include acting as an arylation target of acetaminophen. (Specification, page 2, lines 27-31.) The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. HSEBP is, in that regard, homologous to mouse liver acetaminophen-binding protein (G298710) which is an arylation target of the analgesic acetaminophen and its metabolites following acute drug overdose. Arylation can lead to

life-threatening liver necrosis and to kidney and lung damage. (Specification, page 2, lines 27-31.) In particular, the two polypeptides share 88% sequence identity over 472 amino acid residues.

This is more than enough homology to demonstrate a reasonable probability that the utility of mouse liver acetaminophen-binding protein can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998). (Reference No. 1) Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to mouse liver acetaminophen-binding protein is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this response the Declaration of L. Michael Furness describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 10).

The Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

A. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392,

1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any

showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

B. Uses of the claimed polypeptide for diagnosis of conditions and disorders characterized by expression of HSEBP, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

1. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility

Because there is a substantial likelihood that the claimed HSEBP is functionally related to mouse acetaminophen-binding protein, a polypeptide of undisputed utility, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the claimed polypeptide shares 88 % sequence identity over 472 amino acid residues with mouse acetaminophen-binding protein. This is more than enough homology to demonstrate a reasonable probability that the utility of mouse acetaminophen-binding protein can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. (Brenner et. al., supra, Reference No. 1.) Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to mouse acetaminophen-binding protein is, accordingly, very high.

The Examiner must accept the Applicants' demonstration that the homology between the claimed invention and mouse acetaminophen-binding protein demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Examiner has cited literature (Bowie et al., Burgess et al., Lazar et al., Bork, and Scott et al.) identifying some of the difficulties that may be involved in predicting protein function, none suggest that functional homology cannot be inferred by a reasonable probability in this case. Importantly, none contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

2. The uses of HSEBP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration. The claimed invention is a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a divisional of, and claims priority to, United States patent application Serial No. 09/088,641 filed on June 2, 1998 (hereinafter "the Bandman '641 application"), which in turn was a divisional application of and claimed priority to United States patent application Serial No. 08/749,903 filed on November 15, 1996 (hereinafter "the Bandman '903 application"), having essentially the identical specification, with the exception of corrected typographical errors and reformatting changes.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Bandman '903 application on November 15, 1996 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Bandman '903 application, . . . and other related pre-November 15, 1996 publications, persons skilled in the art on November 15, 1996 clearly would have understood the Bandman '903 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity. . . (Furness Declaration, ¶10)
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> * * *
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> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, page 26).

3. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 2):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 2), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 3); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology - - potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 4).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 5) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information

database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

4. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the sequences of the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the polynucleotide encoding HSEBP. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequence of the claimed polypeptide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

C. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific" or "well established" utilities. (Office Action, page 2.) The Examiner is incorrect both as a matter of law and as a matter of fact.

1. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d

1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Membership in a Class of Useful Products Can Be Proof of Utility

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Examiner addresses HSEBP as if the general class in which it is included is not the selenium-binding protein family and the family of expressed polypeptides, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the selenium-binding protein family and the family of expressed polypeptides do not. The selenium-binding protein family and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that HSEBP would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the selenium-binding protein family and the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the claimed polypeptide is useful.

3. The uses of HSEBP in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include uses in drug screening. (Specification, e.g., at page 38, lines 9-27.)

4. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the applicant cannot impute utility to the claimed invention based on its 96% sequence identity with human fetal heart selenium-binding protein (G1374792; SEQ ID NO:3), its 86% sequence identity with mouse liver selenium-binding protein (G227630; SEQ ID NO:4), and its 88% sequence identity with mouse liver acetaminophen-binding protein (G298710; SEQ ID NO:5). The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

In the present case, the Examiner contended that the degree of amino acid identity among HSEBP, human fetal heart selenium-binding protein (G1374792), mouse liver selenium-binding protein (G227630), and mouse liver acetaminophen-binding protein (G298710) is insufficient to establish that HSEBP is a member of the selenium-binding protein family and thus shares the same utilities. The Examiner attempted to support this assertion with the teachings of Bowie et al., Burgess et al., Lazar et al., Bork, and Scott et al., all of record and addressed below. However, all of these references fail to support the outstanding rejections.

In support of Applicants' use of amino acid sequence homology to reasonably predict the utility of the claimed polypeptide, Applicants provide the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," supra, Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., page 6076). Therefore, the 96% sequence identity with human fetal heart selenium-binding protein (G1374792), the 86% sequence identity with mouse liver selenium-binding protein (G227630), and the 88% sequence identity with mouse liver acetaminophen-binding protein (G298710), over 472 amino acid residues, exceeds the thresholds proposed by Brenner et al., and SEQ ID NO:1 is a true selenium-binding protein by these criteria.

Since these criteria are based on a data set of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved structural and functional characteristics of the selenium-binding protein family. Hence, the "reasonable correlation" standard as set by case law has been met.

Applicants submit that the teachings of Bowie et al. are, in part, counter to the outstanding rejections, and in part, supportive of the asserted utilities of HSEBP based on amino acid sequence homology to human fetal heart selenium-binding protein (G1374792), mouse liver selenium-binding protein (G227630), and mouse liver acetaminophen-binding protein (G298710). Careful review of this reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Applicants' use of amino acid sequence homology to reasonably predict protein function.

In support of Applicants' use of amino acid sequence homology to reasonably predict the utility of the claimed polypeptide, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution (Bowie et al., page 1306, 1st column, last paragraph, and 22nd column, 22nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph). It is known in the art that natural selection acts to conserve protein function. As the Examiner stated and as taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among the claimed polypeptide and known selenium-binding proteins are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would further conclude that the level of conservation observed between the claimed polypeptide and selenium-binding proteins is indicative of a common function, and hence, common utility, among these proteins.

The use of such sequence comparisons to predict protein function is supported by the Bork reference, cited by the Examiner. Bork discloses a 70% accuracy rate in bioinformatics-based predictions. This more than meets the legal standard of utility, which requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% rate for all bioinformatics predictions.

The Examiner cited Scott et al. as further evidence that functional prediction by sequence homology is not reliable. Scott et al. describe a single example in which sequence homology was only partially successful in predicting the protein function of pendrin. In this example, pendrin was correctly identified as an anion transporter by sequence homology. However, the assignment of sulfate as a substrate for pendrin was later found to be incorrect. This one single example of a partially-incorrect functional prediction does not contradict the findings of Bork that, in the majority of cases, protein function is accurately predicted by sequence homology methods. Thus, Scott et al. does not provide any evidence that one of skill in the art would **more likely than not** doubt that HSEBP possesses the utilities of human fetal heart selenium-binding protein (G1374792), mouse liver selenium-binding protein (G227630), and mouse liver acetaminophen-binding protein (G298710).

The Examiner further cited Lazar et al. and Burgess et al. as demonstrating "the sensitivity of proteins to alterations of even a single amino acid in a sequence." (Office Action, page 4.) However, these references are not relevant to the case at hand. Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved among EGFs and TGFs. Similarly, Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. In both of these cases, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. These mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by Lazar et al. and Burgess et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences among SEQ ID NO:1 and human fetal heart selenium-binding protein (G1374792), mouse

liver selenium-binding protein (G227630), and mouse liver acetaminophen-binding protein (G298710) are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of Lazar et al. and Burgess et al. are not relevant to the case at hand.

One could then argue that partial loss-of-function mutations do occur in nature, for example, the mutation in hemoglobin that causes sickle cell anemia. However, this example is the **rare** exception in evolution, **not the rule**. Persistence of such a mutation in a population would **not** be expected by one of ordinary skill in the art. Persistence occurs only because of the fluke of heterozygous advantage. Therefore, the Examiner's assertion that one of skill in the art would routinely expect to find single amino acid substitutions that drastically affect the function of the individual members of a conserved protein family is entirely unsubstantiated. Furthermore, in those rare cases where a partial loss-of-function mutation is persistent, the fact remains that the mutant polypeptide **still retains the utility of the non-mutant polypeptide**. The utility of the mutant polypeptide is the same as that of the non-mutant polypeptide, even though the results achieved are not equivalent. **Some** utility, not **perfect** utility, is all that is statutorily required for patentable utility.

The literature cited by the Examiner is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be withdrawn.

D. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at page 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § I.C.2. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § I.C.2. Thus the Training Materials cannot be applied consistently with the law.

II. Rejection of Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, first paragraph, enablement

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

III. Rejection of Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, second paragraph, alleging that "because the term ["an amino acid sequence"] can encompass any amino acid sequence from two amino acid sequence to a full-length protein." (Office Action, page 8.) In order to expedite prosecution, Applicants have amended Claims 1 and 2 to recite:

> 1. An isolated polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
> b) a polypeptide comprising a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1,
> c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and
> d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.
>
> 2. An isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

IV. Rejection of Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, first paragraph, written description

The Examiner rejected Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, first paragraph, alleging that Applicants were not in possession of the claimed invention. Specifically, the Examiner alleges that "[t]he written description in this case only sets forth SEQ ID NO:1 and therefore the written

description is not commensurate in scope with the claims drawn to a naturally occurring amino acid sequence having at least 96% sequence identity to SEQ ID NO:1, biologically active fragments of SEQ ID No:1 or immunogenic fragments of SEQ ID No:1." (Office Action, page 9.)

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 is specifically disclosed in the application (see, for example, Sequence Listing, pages 49-50). Variants of SEQ ID NO:1 are described, for example, at page 6, lines 9-12 and lines 19-27 and page 13, lines 7-10. In particular, the preferred, more preferred, and most preferred SEQ ID NO:1 variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are described, for example, at page 13, lines 7-10. Incyte clones in which the nucleic acids encoding the human HSEBP were first identified and libraries from which those clones were isolated are described, for example, at page 12, lines 13-20 of the Specification. Chemical and structural features of HSEBP are described, for example, on page 12, lines 21-34. Given SEQ ID NO:1, one of ordinary skill in the

art would recognize naturally-occurring variants of SEQ ID NO:1 at least 96% identical to SEQ ID NO:1. The Specification describes (e.g., page 40, line 34 through page 41, line 19) how to use BLAST to determine whether a given sequence falls within the "at least 96% identical" scope. Biologically active fragments are described in the Specification, e.g., at page 7, lines 5-6. Immunogenic fragments are described in the Specification, e.g, at page 7, lines 6-9, page 26, lines 17-23, and page 46, line 26 through page 47, line 10. Accordingly, the Specification provides an adequate written description of the recited polypeptides.

There simply is no requirement that the claims recite particular variant and fragment polypeptide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants and fragments are defined in terms of SEQ ID NO:1 ("An isolated polypeptide selected from the group consisting of: a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, b) a polypeptide comprising a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1, c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." Because the polypeptide variants and fragments are defined in terms of SEQ ID NO:1, the precise chemical structure of every polypeptide variant and fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention. Applicants further submit that given the polypeptide sequence of SEQ ID NO:1, it would be redundant to list specific fragments. The structure of SEQ ID NO:1 provides the blueprint for all fragments thereof. Listing all possible fragments of SEQ ID NO:1 is, thus, a superfluous exercise which would needlessly clutter the Specification. Accordingly, the Specification provides an adequate written description of the recited polypeptides.

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue which are hence relevant to claims to proteins encoded by the DNA commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

If a conception of a DNA requires a precise definition, such as by structure, formula,

> chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than

on functional characteristics. For example, the "variant language" and "fragment language" of independent claim 1 recite chemical structure to define the claimed genus:

> 1. An isolated polypeptide selected from the group consisting of. . .
>
> b) a polypeptide comprising a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1,
>
> c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and
>
> d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides recited by the claims. Such functional recitations that are included add to the structural characterization of the recited polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." (Office Action, page 11.) Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," supra, Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and

6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to human selenium-binding proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as human selenium-binding proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polypeptides encoding "a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 472 amino acid residues). This variation is far less than that of all potential human selenium binding proteins related to SEQ ID NO:1, i.e., those human selenium binding proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of November 15, 1996. Much has happened in the development of recombinant DNA technology in the 16 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants and fragments at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

CONCLUSION

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[2] to target rejections of claims to polypeptides and polynucleotides where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established,

[2]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

specific, substantial and credible utilities. The rejections are, therefore, improper and should be withdrawn.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 845-4646.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE GENOMICS, INC.

Date: December 17, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 12, line 13, has been amended as follows:

Nucleic acids encoding the HSEBP of the present invention were first identified in Incyte Clone 989953 from the colon cDNA library (COLNNOT11) through a computer-generated search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:2, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 989953 (COLNNOT11), 609011, 1226183, and 1227155 (COLNNOT01), 1334268 (COLNNOT13), 1284686 (COLNNOT16), 1391936 (THYRNOT03), (COLNNOT01), 959734 (BRSTTUT03), 892480 (STOMTUT01), and 814959 (OVARTUT01).

Paragraph beginning at page 12, line 21 and ending on page 13, line 6, has been amended as follows:

In one embodiment, the invention encompasses the novel human selenium-binding protein, a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Fig. 1A,B,C. HSEBP is 472 amino acids in length and has no predicted transmembrane domains, potential glycosylation or phosphorylation sites. HSEBP is enriched in leucine and glycine residues which together constitute more than 20% of the total amino acid content. As shown in Fig. 1A,B,C, there are no in-frame TGA termination codons in the nucleic acid sequence of SEQ ID NO:2 to direct the incorporation of selenocysteine into the protein of SEQ ID NO:1. HSEBP has chemical and structural homology with the human fetal heart selenium-binding protein (G1374792 [G1374972]; SEQ ID NO:3), mouse liver selenium-binding protein (G227630; SEQ ID NO:4), and mouse liver acetaminophen-binding protein (G298710; SEQ ID NO:5). In particular, HSEBP shares 96%, 86%, and 88% identity, respectively, with each of these proteins. As illustrated by Figs. 3 and 4, HSEBP and human fetal heart selenium-binding protein have rather similar hydrophobicity plots. Their isoelectric points, 5.91 and 6.13, respectively, are also similar. Northern analysis (Fig. 5) shows the expression of the HSEBP sequence

in various libraries. Approximately 50% of these libraries are from cancerous tissues and 38% are from the gastrointestinal tract.

IN THE CLAIMS:

Claims 1, 2, and 14 have been amended as follows:

1. (Once Amended) An isolated polypeptide [comprising an amino acid sequence] selected from the group consisting of:

a) a polypeptide comprising the [an] amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally-occurring amino acid sequence [having] at least 96% identical [sequence identity] to the amino acid sequence of SEQ ID NO:1,

c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

2. (Once Amended) An isolated polypeptide of claim 1, comprising the amino acid [having a] sequence of SEQ ID NO:1.

14. (Once Amended) A composition of claim 13, wherein the polypeptide comprises [has] the amino acid sequence of SEQ ID NO:1.